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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,342	07/27/2000	DAVID J. CLARKE	39-206	8022

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EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/529,342	CLARKE ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-68* is/are pending in the application.

4a) Of the above claim(s) *43,44,53,62,63,67 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45-52,54-61 and 64-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment of claim 64 is acknowledged and has been enetered.

2. Claims 42, 45-52, 54-61, 64-66 are currently under examination.

3. Claims 43-44, 53, 62-63, 67-68 have been withdrawn.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 42, 45-49, 51, 52, 54, 55, 58, 61, 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728].

6. With respect to claims 42, 51, 52, 64, Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20). Meers et al further teach that the liposomes of this invention can incorporate a species activated on modulation of permeability (column 9, lines 25-48), comprising one or more "bioactive agents," which are compounds or compositions of matter having biological, including therapeutic or diagnostic, activity in animals (column 9, lines 25-

48), and which include dyes and radiolabels (column 9, lines 40-50) and fluorescent labels (column 20, lines 51-62). The particles can be used to deliver diagnostically effective amounts of diagnostic agents into the cells of a mammal afflicted with a disease, disorder, or condition (column 10, lines 59-65). Meers et al further teach monitoring the fluorescence (column 20, lines 60-62). Meers et al do not teach the use of liposomes that incorporate cytolytic peptides such as GALA which interacts with the layer to act as or mediate the opening of pores or channels.

Parente et al, however, do teach the use of liposomes GALA (p.8720, col.1, lines 12-26), and further teaches that GALA assembles to form a pore or channel (lysing the lipid vesicle), leakage is rapid and complete (p.8726, col. 2, lines 4-17). Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the peptide of Meers et al with the GALA of Parente et al, as Meers et al disclose a higher level of liposome binding to cells at pH 4.0 than at pH 7.4 (col. 20, lines 51-67), while Parente et al disclose that 100% leakage occurs at pH 5, while leakage is halted at pH 7 (p.8724, col.1, lines 1-20). Since the amino acid sequence of GALA and N, Myristic GALA is essentially the same, with similar functions and pH sensitivities, GALA would be functionally equivalent to N, Myristic GALA and therefore it would be obvious to utilize GALA or N, Myristic GALA, in order permit rapid and complete leakage when GALA lyses the lipid vesicles.

Therefore it would be obvious to utilize liposomes comprising a cytolytic peptide such as GALA or N, Myristic GALA in the method of Meers et al, in order to modulate the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type, as taught by Parente et al, in order permit rapid and complete leakage.

7. With respect to claim 45, Parente et al. teach the use of GALA (p.8720, col.1, lines 12-26), and further teaches that once GALA assembles to form a pore or channel (lysing the lipid vesicle).

8. With respect to claims 46-47, Meers et al teach that the liposomes can comprise a targeting moiety such as antibodies that can direct the liposomes to specific sites within the body of a mammal (column 8, lines 3-20).

9. With respect to claims 48-49, Meers et al teach that liposomes can comprise glycoprotein streptavidin (second binding moiety) which can be used to link proteins (first binding moiety) (column 9, lines 20-25). Aggregation would occur when multiple liposomes bind to the same cell of interest.

10. With respect to claims 54-55, Meers et al teach that the species can be a dye or an enzyme (column 9, lines 25-48).

11. With respect to claims 58 and 61, Meers et al teach that the liposome can be used for diagnostic activity in animals (column 9, lines 25-29).

12. With respect to claims 65-66, Parente et al teach that leakage of the vesicles would occur as the pH is changed from a pH of 7.3 to pH of 5 (p.8723, col.2, lines 21-26, fig. 2B). Meers et al further teach that binding of liposomes to cells of interest increase at changes of pH to around 4 (col. 20, lines 51-67).

13. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and in light of Li et al [US 5,512,294].

With respect to claims 50, Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al further teach that liposomes can comprise glycoprotein streptavidin (second binding moiety) which can be used to link proteins (first binding moiety) (column 9, lines 20-25). Meers et al do not specifically teach using biotin as the second binding moiety.

Li et al do, however, demonstrate that teach liposomes where avidin is used to bind proteins such as antibodies, the antibodies are attached by the biotin-avidin biotinylated antibody sandwich (fig.16, column 9, lines 65-67). One of ordinary skill in the art would therefore realize to attach proteins to streptavidin, they would need to biotinylate the proteins.

14. Claims 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and further in view of Levinson et al [US 6,020,142].

With respect to claims 56-57, Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al teach that the species can be a

dye or an enzyme (column 9, lines 25-48). Meers et al do not teach that the species is a substrate for an enzyme or is glucose oxidase.

Levinson et al, however, teach the use of a delivery complex such as liposomes (column 3, lines 5-12) for delivering enzymes and substrates such as glucose oxidase (column 25, lines 40-42) in order to label RATH gene peptide-specific antibodies. This is important as the RATH1.1 gene product has been demonstrated to act as a mediator of signal transduction events, and and the detection of compounds which modulate the RATH gene product would allow for the diagnostic evaluation, prognosis, and treatment of immune disorders involving T cell activation (column 1, lines 29-62).

Therefore one of ordinary skill in the art would have been motivated to have the liposomes deliver enzymes and substrates such as glucose oxidase, as suggested by Levinson et al, in the method of Meers et al and Parente et al, to in order to study specific cells such as T cells, such that the diagnostic evaluation, prognosis, and treatment of immune disorders involving T cell activation is possible.

15. Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and further in view of Robinson et al [US 5,994,149].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability

(column 9, lines 25-48). Meers et al further teach that the liposome can be used for diagnostic activity in animals (column 9, lines 25-29). Meers et al do not teach the detection of pathogenic cells in foodstuffs.

Robinson et al, however, do teach the analysis of foodstuffs for pathogenic cells using liposomes (column 4, lines 19-24). Robinson et al further teach that it would be desirable to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, yeasts and molds (column 1, lines 16-45).

Therefore it would be obvious to teach the detection of pathogenic cells in foodstuffs, as taught by Robinson et al, in the method of Meers et al and Parente et al, in order to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, yeasts and molds.

16. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and further in view of Blondin et al [US 4,808,517].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al further teach that the liposome can be used for diagnostic activity in animals (column 9, lines 25-29). Meers et al do not teach the detection of pathogenic cells in foodstuffs. Meerss et al do not teach the detection of pathogenic cells in water samples.

Blondin et al, however, do teach a method of using of lipid vesicles (column 4, lines 9-24) for the detection of toxins in water samples (column 8, lines 20-32) that is economical and efficient and can be quickly and easily performed (column 2, lines 64-68).

Therefore it would be obvious to use the method of Meers et al and Parente et al to analyze water samples for pathogens as taught by Blondin et al, in order to detect toxins economically, efficiently, quickly and easily.

Response to Arguments

17. Applicant's arguments filed January 25, 2007 have been fully considered but they are not persuasive.

It is noted that although Meers et al. do discuss a method of treating diseases, Meers et al. also teach a method involving liposomes with bioactive agents such as fluorescent compounds (column 9, lines 40-44) and monitoring the amount of fluorescence released (column 20, lines 60-62). The Office acknowledges that Parente et al. do discuss the production of vesicles having a "detectable content".

18. With respect to applicant's arguments regarding Parente et al., applicant argues on p. 9 that Parente et al. do not start with liposomes that incorporate GALA, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., starting with liposomes that incorporate GALA) are not recited in the rejected claim(s), and applicant never discusses or recites how the liposomes start with incorporated GALA. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988

F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Claim 1 merely recites that the liposomes incorporating a cytolytic peptide. Since Parente et al. teach that to induce the same extent of leakage at pH 6, the peptide concentration must be increased over 10 fold, and at pH 7.5, the extent of leakage never becomes greater than 30%, whereas at pH 5, 100% leakage occurs (p.8724, col.2). Since leakage is dependant on the amount of cytolytic peptide incorporated into the liposomes, as can be seen, Parente et al. do teach that GALA does get incorporated at with the lipid membranes when at neutral pH, abeit at lower levels. Furthermore, since applicant has not recited how the cytolytic peptides are incorporated into the liposomes, applicant's arguments are not found persuasive.

19. In fact, since applicant has not recited how the cytolytic peptides are incorporated into the liposomes, one of ordinary skill in the art would reasonably assume that the method taught by Parente et al. is the only way to incorporate the cytolytic peptides into the liposomes.

20. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

21. With respect to applicant's arguments regarding the remaining rejections, they appear to refer to applicant's arguments regarding Parente et al. and Meers et al., which has been discussed above.

Conclusion

22. No claims are allowed.

23. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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